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A Controlled Study of Tourette Syndrome. III. Phobias and Panic Attacks

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SUMMARY

Comparison was made of the frequency of phobias and panic attacks in normal controls and in patients with Tourette syndrome (TS), attention-deficit disorder (ADD), and ADD secondary to a *TS* gene. For phobias the most significant difference between controls and TS patients was with respect to fear of public transportation ($P = .002$), followed by fear of being alone ($P = .009$), fear of being in a crowd ($P = .01$), fear of being in water ($P = .025$), fear of animals ($P = .04$), fear of public speaking ($P = .05$), and other fears ($P = .05$). Only 8.5% of controls had more than three simple phobias and none had more than five, whereas 26% of TS patients had more than three ($P = .008$) and some had as many as 13. As opposed to 19% of TS patients, none of the controls had phobias that interfered with their life ($P = .001$). Among female TS patients 55.1% had 3–13 phobias, compared with 8.7% of the female controls ($P < .0005$). There was no correlation between the ADD score and the number of phobias ($r = -.010$) and little correlation with the total number of tics ($r = .14$). Panic attacks were present in 8.3% of the controls and 33% of the TS patients ($P = .0008$). This frequency increased to 55.2% ($P < .0005$) for grade 3 (severe) TS patients. None of the controls, 15.9% of all TS patients ($P = .002$), and 31% of grade 3 TS patients ($P < .0005$) had more than three panic attacks in 1 wk. Total panic-symptom score (12 possible symptoms) was significantly greater than that in the controls in all grades of TS. The presence or absence of ADD had little effect on the total panic-symptom score, but the presence of ADD resulted in a significantly lower average age at onset of panic attacks (8.8 years) compared with those TS patients without ADD (15.4 years) (*P*

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= .03). These observations indicate that phobias and panic attacks are a significant part of the symptomatology of TS and provide the first clear indication that phobias and panic attacks can be due to the presence of a major gene.

INTRODUCTION

DSM III (1980) defines a simple phobia as a persistent, irrational fear of and compelling desire to avoid an object or situation to the extent that it causes significant distress and interferes with life. The individual recognizes that his or her fear is excessive or unreasonable. Other than agoraphobia (Comings and Comings 1987*c*), phobias have rarely been described in association with Tourette syndrome (TS). The use of the comprehensive Diagnostic Interview Schedule (DIS) (Robins et al. 1981) allowed us to investigate whether patients with TS had a significantly greater frequency of phobic symptoms than did a control population.

Panic attacks are manifested by the sudden onset of feelings of intense fear and anxiety. They are episodic in nature and, as such, are distinct from generalized anxiety disorder, which is characterized by persistent anxiety of at least 1 mo duration (DSM III 1980).

The first hint that panic attacks may be an associated feature of TS came from the study by Montgomery et al. (1982) of the first-degree relatives of 15 TS patients. Although none of the probands were listed as having panic attacks, four of the 30 first-degree relatives had panic attacks. The second clue came from a study of Comings and Comings (1987*c*), who found that panic attacks associated with agoraphobia were present in 10% of the adult female first-degree relatives of TS probands and could be the only symptom of an individual carrying the *TS* gene. This led us to investigate the frequency of panic attacks in TS patients themselves.

METHODS

The general elements of this controlled study have been described in Part I (Comings and Comings 1987*a*). The DIS questions concerning phobias are the following: "Some people have phobias, that is, such a strong fear of something or some situation that they try to avoid it, even though they know there is no real danger. Have you ever had such an unreasonable fear of the following situations that you tried to avoid it/them?" (see table 1 for the individual items). Ancillary questions were as follows: "If any of the above are yes, does attempting to avoid these situations interfere with your life, for example, keep you from going places or doing things you would otherwise do?" "If any of the above were answered yes, do you feel these are reasonable or unreasonable fears?"

To determine whether the controls or patients had panic attacks, the following questions from the DIS were asked: "Have you ever had a spell or attack

TABLE 1

PHOBIAS

	Diagnostic Category (*N*)								
		TS							
	Controls (47)	All Cases (246)	Grade 1 (43)	Grade 2 (145)	Grade 3 (58)	+ADD (152)	−ADD (94)	ADD (17)	ADD 2⁰ TS (15)
A. Data for Individual Phobias									
Fear of									
Heights:									
%	18.7	26.8	20.9	28.3	27.6	21.7	35.1	25.0	13.3
χ^2	...	1.36	0.069	1.70	1.14	0.20	4.04	0.30	0.23
P	...	.25	.80	.19	.29	.66	**.05**	.59	.63
Tunnels or bridges:									
%	4.2	11.4	11.6	10.3	13.8	7.8	17.0	6.2	0.0
χ^2	...	2.22	1.72	1.64	2.78	0.73	4.62	0.11	0.65
P	...	.14	.19	.20	.09	.39	**.03**	.74	.42
Being in a crowd:									
%	2.1	15.8	13.9	13.8	22.4	14.5	18.1	6.3	0.0
χ^2	...	6.30	4.38	5.00	9.27	5.39	7.20	0.71	0.32
P	...	**.01**	**.04**	**.02**	**.001**	**.02**	**.008**	.41	.57
Being on any kind of public transportation:									
%	2.1	19.1	11.6	17.9	27.6	17.8	21.3	12.5	0.0
χ^2	...	8.32	3.27	7.35	12.4	7.31	9.1	2.92	0.32
P	...	**.002**	.07	**.006**	**<.0005**	**.007**	**.002**	.09	.57
Going out of the house alone:									
%	4.2	10.2	4.6	10.3	13.8	7.2	14.9	0.0	0.0
χ^2	...	1.69	0.008	1.64	2.78	.53	3.57	0.74	0.65
P	...	.19	.93	.20	.09	.47	.06	.41	.42
Being alone:									
%	8.3	26.0	23.3	24.1	32.7	29.0	21.3	12.5	20.0
χ^2	...	6.95	3.86	5.49	9.07	8.41	3.76	0.25	1.58
P	...	**.009**	**.05**	**.02**	**.002**	**.002**	**.05**	.62	.21

TABLE 1 (Continued)

	Diagnostic Category (*N*)								
		TS							
	Controls (47)	All Cases (246)	Grade 1 (43)	Grade 2 (145)	Grade 3 (58)	+ADD (152)	−ADD (94)	ADD (17)	ADD 2° TS (15)
A. Data for Individual Phobias									
Fear of									
Eating in front of other people or in public:									
%	6.2	8.5	4.6	9.0	10.3	8.5	8.5	6.2	0.0
χ^2	...	0.28	0.11	0.37	0.56	0.26	0.23	0.0	0.97
P	...	.60	.74	.54	.45	.61	.63	...	.32
Speaking in front of a small group of people one knows:									
%	10.4	22.8	18.6	19.3	34.8	26.3	17.0	18.7	0.0
χ^2	...	3.68	1.23	1.98	8.50	5.19	1.08	0.78	1.69
P	...	**.05**	.27	.16	**.002**	**.02**	.29	.38	.19
Speaking to strangers or meeting new people:									
%	18.7	26.4	23.3	24.8	32.8	25.0	28.7	12.5	13.3
χ^2	...	1.24	0.29	0.74	2.65	0.79	1.65	0.34	0.23
P	...	.27	.59	.38	.10	.37	.20	.57	.63
Being in a closed place:									
%	16.7	23.2	20.9	19.3	34.5	21.1	26.6	6.2	6.7
χ^2	...	0.99	0.26	0.16	4.22	0.43	1.72	1.14	0.93
P	...	.35	.77	.47	.10	.41	.29	.38	.76
Storms:									
%	10.4	15.8	11.6	14.5	22.4	15.1	17.0	18.8	13.3
χ^2	...	0.90	0.033	0.51	2.65	0.66	1.08	0.80	0.097
P	...	.32	.77	.47	.10	.41	.29	.38	.76

Being in water:									
%	2.1	13.4	11.6	13.8	13.8	11.2	17.0	6.2	13.3
χ^2	...	4.92	3.27	5.00	4.54	3.61	6.57	0.68	3.11
P	...	**.025**	.07	**.025**	**.03**	**.06**	**.01**	.41	.08
Spiders, bugs, mice, snakes, or bats:									
%	27.0	31.7	23.3	32.4	36.2	25.7	41.5	12.5	26.7
χ^2	...	0.41	0.16	0.48	1.00	0.03	2.83	1.47	0.0005
P	...	.52	.69	.48	.31	.76	.09	.24	.99
Being near any other harmless animal or dangerous animals that could not get to one:									
%	2.1	12.6	14.0	10.3	17.2	11.2	14.9	0.0	0.0
χ^2	...	4.47	4.40	3.2	6.35	3.61	5.40	0.36	0.32
P	...	**.04**	**.04**	.08	**.01**	.06	**.02**	.56	.57
Other:									
%	6.2	17.9	7.0	19.3	22.4	19.1	16.0	18.7	6.7
χ^2	...	4.01	0.023	4.51	5.30	4.45	2.70	2.26	0.003
P	...	**.05**	.75	**.03**	**.02**	**.04**	.10	.14	.95

B. Data for Phobias in Combination

Criterion									
Phobia score >3:									
%	8.5	26.0	27.9	29.6	37.9	28.3	36.2	12.5	20.0
χ^2	...	6.78	5.78	8.56	12.05	7.86	12.2	0.23	1.50
P	...	**.009**	**.018**	**.002**	**.0005**	**.005**	**<.0005**	.64	.22
Interference with normal life and phobia score >3:									
%	0.0	19.1	11.6	17.9	31.1	19.7	20.2	12.5	6.7
χ^2	...	10.7	5.77	9.72	17.6	10.9	11.0	6.07	3.20
P	...	**.001**	**.018**	**.001**	**<.0005**	**.001**	**.001**	**.015**	.08

NOTE.—Significant *P* values are boldface.

(not due to a physical illness) when all of a sudden you felt frightened, anxious, or very uneasy in situations where most people would not be afraid?" "If yes, how many such attacks have you had in your life?" "If yes, during one of your worst spells, which of the following problems were present?" (see table 2). "If yes, have you ever had three spells like these close together, that is, within a three-week period?" "If yes, and if you also had some of the phobias listed, have the phobias and the anxiety attacks sometimes occurred together (i.e., at the same time?)"

RESULTS

Table 1 shows the results of the questions concerning individual phobias. For no diagnostic category were the fear of going out of the house alone, of eating in front of other people or in public, of speaking to strangers or meeting new people, of being in a closed place, of storms, and of spiders, bugs, mice, snakes, or bats significantly different from those of controls. Fear of heights and of tunnels or bridges were significantly different only for TS patients without ADD ($P = .04$ and .03). Fear of public transportation, fear of being in water, and other phobias were significantly different for all grades of TS except grade 1. Differences in fear of animals and of speaking in front of a small group of people that one knows were significantly different for all TS patients but not for all grades of TS. Fear of being in a crowd and of being alone were significantly different for all subtypes of TS. The fear of being alone was the one fear that we had detected most often in nonstructured discussions with TS patients and their parents. Separation anxieties at the start of preschool years were often mentioned, and even later in life many TS patients express severe fears of being left alone. One-third of grade 3 TS patients expressed this fear, as did 23% of grade 1 TS patients. None of either the ADD patients or the patients with ADD secondary to TS (ADD 2^0 ADD) had any phobias that were significantly greater in frequency than they were in the controls. This fact may represent the younger average age of these groups (Comings and Comings 1987*a*).

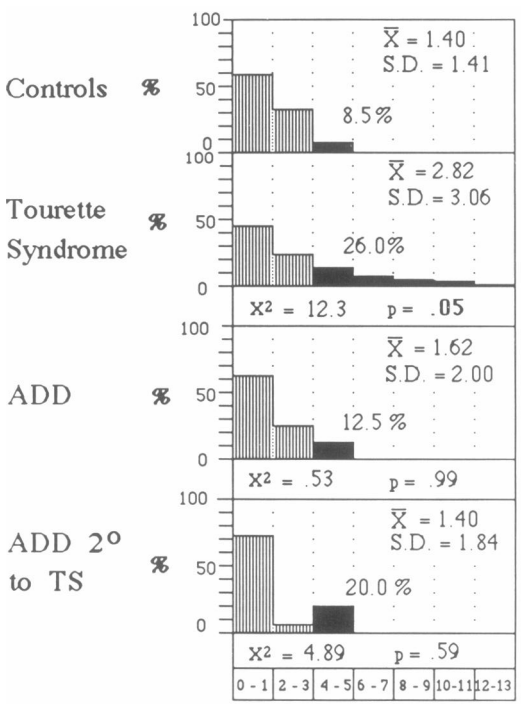
The number of different phobias in TS patients was generally more impressive than the frequency of individual phobias. A phobia score was derived by adding a 0 for each no and a 1 for each yes (fig. 1). Only 8.5% of the control population had more than three phobias and none had more than five, whereas 26% of all TS patients had three or more phobias, with total numbers as high as 13 ($P = .009$; df = 1). The phobia scores were not significant for ADD or ADD 2^0 TS patients. Among the different grades of TS, only grade 3 had scores significantly different than those in controls (when as many as 6 df were used for the whole range of scores). However, χ^2 values derived from simply comparing the percent of patients with phobia scores >3 gave highly significant differences for all diagnostic categories except ADD and ADD 2^0 TS (table 1). The χ^2 values were higher for TS patients without ADD than for those with ADD. This is consistent with the fact that the correlation coefficient between the ADD score (Comings and Comings 1987*a*) and phobia score was $-.010$ and that that between the ADDH score and phobia score was $-.008$. There was little corre-

TABLE 2

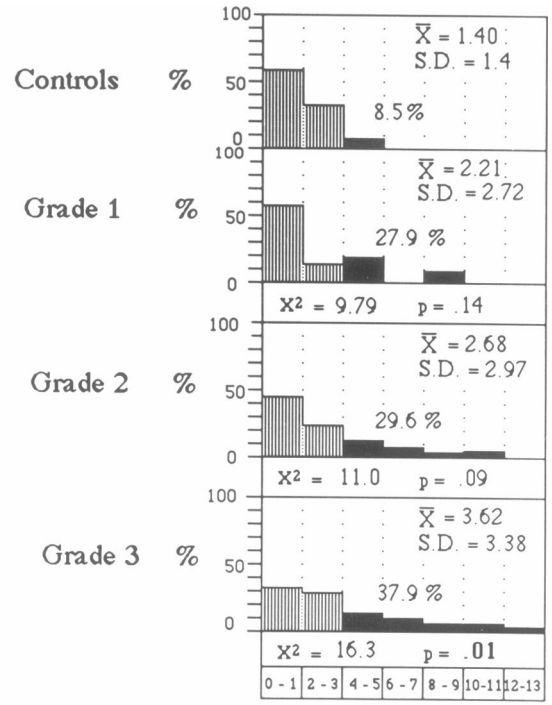
PANIC ATTACKS

PARAMETER	DIAGNOSTIC CATEGORY								
		TS							
	Controls	All Cases	Grade 1	Grade 2	Grade 3	+ADD	−ADD	ADD	ADD 2^0 TS
Panic attacks:									
%	8.3	33.0	17.0	30.3	55.1	37.5	25.5	18.7	13.3
χ^2	...	11.9	1.56	9.35	25.6	14.7	5.95	1.33	0.33
P	...	**.006**	.2	**.002**	**<.0005**	**<.0005**	.016	.25	.59
≥3 Attacks/wk:									
%	0.0	15.8	7.0	12.4	31.0	17.1	13.8	0.0	0.0
χ^2	...	8.74	3.47	6.56	17.9	9.43	7.29	...	...
P	...	**.002**	.07	**.01**	**<.0005**	**.0015**	**.007**	...	...
Phobias and panic attacks together:									
%	4.2	14.2	4.7	11.7	27.6	15.8	11.7	17.1	13.8
χ^2	...	3.65	0.01	2.28	10.1	4.37	2.15	2.90	1.73
P	...	.06	.92	.14	**.001**	**.04**	.15	.09	.19

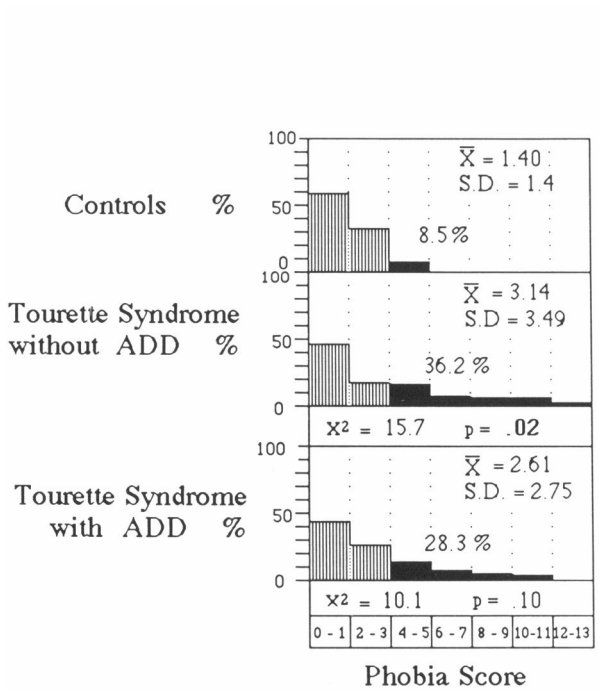
NOTE.—Significant *P* values are boldface.


Controls %
X̄ = 1.40
S.D. = 1.41
8.5%
Tourette Syndrome %
X̄ = 2.82
S.D. = 3.06
26.0%
X² = 12.3 p = .05
ADD %
X̄ = 1.62
S.D. = 2.00
12.5 %
X² = .53 p = .99
ADD 2° to TS %
X̄ = 1.40
S.D. = 1.84
20.0 %
X² = 4.89 p = .59
100
50
0
0 - 1
2 - 3
4 - 5
6 - 7
8 - 9
10-11
12-13
Phobia Score

A


Controls %
X̄ = 1.40
S.D. = 1.4
8.5%
Grade 1 %
X̄ = 2.21
S.D. = 2.72
27.9 %
X² = 9.79 p = .14
Grade 2 %
X̄ = 2.68
S.D. = 2.97
29.6 %
X² = 11.0 p = .09
Grade 3 %
X̄ = 3.62
S.D. = 3.38
37.9 %
X² = 16.3 p = .01
100
50
0
0 - 1
2 - 3
4 - 5
6 - 7
8 - 9
10-11
12-13
Phobia Score

B



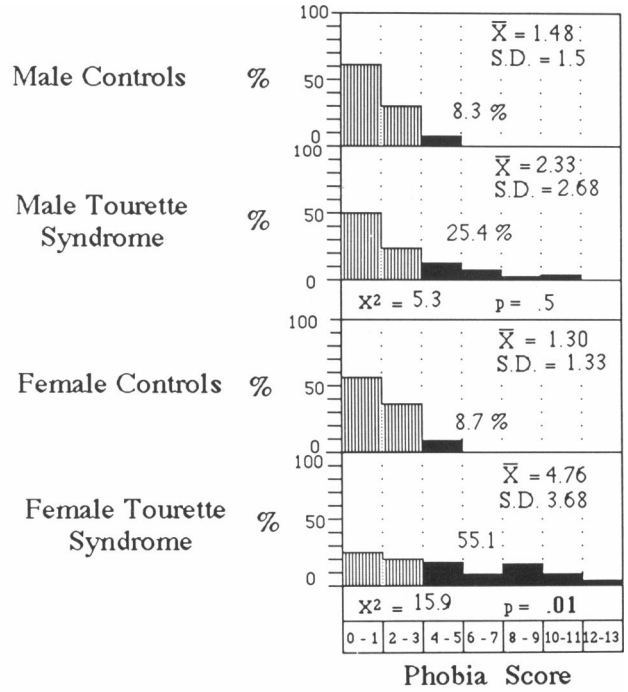


FIG. 1.—Phobia score in different patient groups. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls vs. the three grades of TS patients; *C*, controls vs. TS patients without and TS patients with ADD; *D*, male controls vs. male TS patients and female controls vs. female TS patients. The χ^2 values are based on the numbers of df required for comparing the percent of patients in the different score groups. By contrast, χ^2 values based on 1 df for comparing the percent of patients with phobia scores >3 give much lower *P* values (see table 1).

lation between the number of simple phobias and the number of tics ($r = .14$). Since phobias are often more common in females, the TS males and TS females were analyzed separately. This analysis revealed that 8.3% of male controls and 25.4% of male TS patients had more than three phobias ($P = .34$; df = 1), whereas 8.7% of female controls and 55.1% of female TS patients had more than three phobias ($P < .0005$; df = 1).

Of those individuals with more than three phobias, none in the control group felt that their phobias significantly interfered with life, whereas 19.1% of the TS patients stated that the phobias so interfered ($P = .001$). This frequency increased to 31.1% ($P < .0005$) for the grade 3 TS patients. Again, there was no difference for those patients with ADD (19.7%), compared with those without ADD (20.2%). In all diagnostic categories, ~50% of individuals with more than three simple phobias felt that the fears were unreasonable.

Among the controls, 8.3% had panic attacks, compared with 33% of all TS patients ($P = .0008$) (table 2). The occurrence of panic attacks increased progressively with the grade of TS, with 17% of grade 1 (mild), 30.3% of grade 2 (moderate), and 55.1% of grade 3 (severe) TS patients affected. Of the TS patients with ADD, 37.5% had panic attacks ($P < .0005$), whereas 25.5% of TS patients without ADD had panic attacks ($P = .02$). Neither the patients with ADD nor those with ADD associated with a TS gene had significantly more panic attacks than did controls. None of the controls, compared with 15.8% of the TS patients ($P = .002$), had three or more panic attacks in 1 wk ($P = .002$). This frequency increased from 7% for grade 1 and 12.4% for grade 2 to 31% for grade 3 TS. Both TS patients with ADD (17.1%; $P = .0015$) and TS patients without ADD (13.8%; $P = .007$) had significantly more panic attacks by this criterion than did controls. The existence of phobias and panic attacks together did not quite attain significance for all TS patients (14.2%) when compared with controls (4.2%) ($P = .06$). In grade 3 TS patients, 27.6% had phobias and panic attacks together ($P = .001$).

The total number of panic attacks is shown in figure 2. These figures are slightly lower than those in table 2 because not everyone stating he or she had panic attacks answered the question about how many. Of those who did answer this latter question, 6.4% of the controls had one or more panic attacks and none had more than 99. By comparison, 27.2% of the TS patients had one or more panic attacks and 8% had more than 99 ($P = .002$). The frequencies for the ADD and ADD 2^0 TS groups were not significantly different from that in controls. The number of panic attacks in the three grades of TS are illustrated in figure 2*B*. Even in grade 1 TS patients, 7% had 99 or more attacks. There was little difference in the frequency profiles for TS patients with and without ADD (fig. 2*C*).

The results in relation to the individual symptoms of panic attacks are shown in table 3. In virtually every case, the frequency of any individual symptom was significantly greater for all TS patients and for grade 2 and grade 3 TS patients than that for the controls. Except for choking sensation and excessive sweating, all grade 3 TS patients were different from controls at $P \leq .0005$. The grade

1 TS patients were significantly different from controls only for the symptoms of feeling unreal and thinking that they might die.

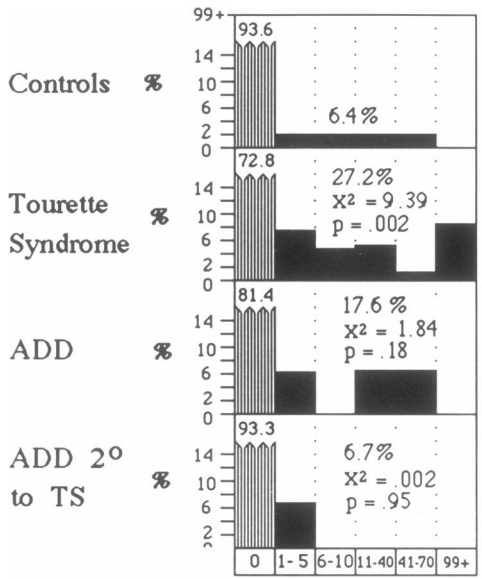
To further evaluate the differences between controls and TS patients, we counted the number of different panic-attack symptoms (from table 3) in each patient to give a panic score with a minimum value of 0 and a maximum value of 12. The distribution of these scores in the different diagnostic groups is shown in figure 3. Only 2.1% of controls had a score ≥ 3 (average 0.21), compared with 28.8% of TS patients (average 2.0; $t = 3.84$; $P = .001$). The maximum score in the controls was 4, whereas the maximum in the TS patients was 12. In the ADD patients, 5.9% had scores >3 (average 0.87), and all were in the 11–12 range. In the ADD 2^0 TS group, 13.3% had a score >3 and again all were in the 11–12 range. Neither of these groups was different from the controls by either χ^2 of the distribution or *t*-test of the means. The percent of patients with scores >3 progressively increased from 18.6% for grade 1 and 21.1% for grade 2 to 55% for grade 3 TS patients (fig. 3*B*). By *t*-test the means in all three grades were significantly different from that in controls. Among TS patients without ADD, 27.6% had a panic score >3, whereas this was the case in 29.5% of TS patients with ADD (fig. 3*C*). Both groups were significantly different from controls by both χ^2 of the distribution and *t*-test of the means. There were no significant differences in the distribution of the panic score for male versus female TS patients.

The average age at onset of panic attacks is shown in table 4; it was 22.7 years for the three controls with panic attacks and dropped to 11.0 years for all TS patients. This difference was almost significant ($P = .06$). Even in grade 3 TS, the average age at onset, 11.4 years, was not significant ($P = .12$). However, if the TS patients were to be divided into those with and without ADD, the average age at onset of panic attacks in those with ADD was 8.8 years. This is significantly different from age at onset in the controls ($P < .001$). The age at onset for those without ADD was 15.4 ($P = .44$). These patients were significantly different from each other at $P = .03$. Thus, although the presence of ADD only moderately affected the percentage of patients with panic attacks, it significantly decreased the mean age at onset of panic attacks.

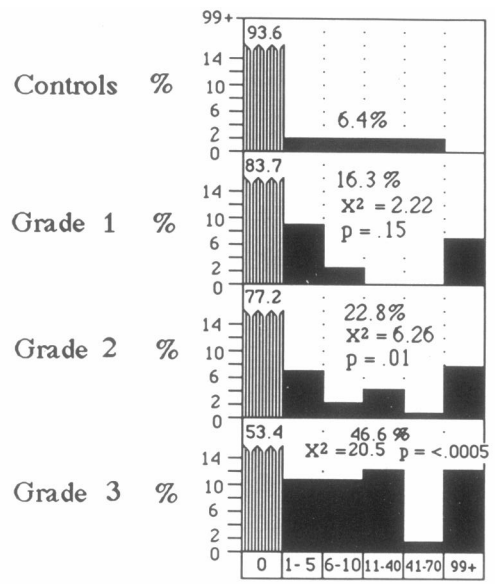
DISCUSSION

Epidemiological studies of the simple phobias, also with use of the DIS, indicate a population prevalence of 7% (Robins et al. 1984). This is not significantly different from the 8% frequency in our controls with a phobia score >3. Most of the studies on the genetics of phobias have centered around agoraphobia, which is more closely related to panic attacks than are simple phobias. School phobia is also common in TS, both before (Comings and Comings 1987*a*) and after the use of haloperidol (Mikkelsen et al. 1981; Linet 1985).

Although some of the phobias, such as fear of being in a crowd, of public transportation, and of public speaking, might be construed as TS patients simply preferring isolation because of the presence of motor and vocal tics, in many cases these were true phobias and persisted even when the tics were well


Controls %
Tourette Syndrome %
ADD %
ADD 2° to TS %
99+
14
10
6
2
0
93.6
6.4%
72.8
27.2%
X² = 9.39
p = .002
81.4
17.6 %
X² = 1.84
p = .18
93.3
6.7%
X² = .002
p = .95
0
1-5
6-10
11-40
41-70
99+
Number of Panic Attacks

A


Controls %
Grade 1 %
Grade 2 %
Grade 3 %
99+
14
10
6
2
0
93.6
6.4%
83.7
16.3 %
X² = 2.22
p = .15
77.2
22.8%
X² = 6.26
p = .01
53.4
46.6 %
X² =20.5 p = <.0005
0
1-5
6-10
11-40
41-70
99+
Number of Panic Attacks

B

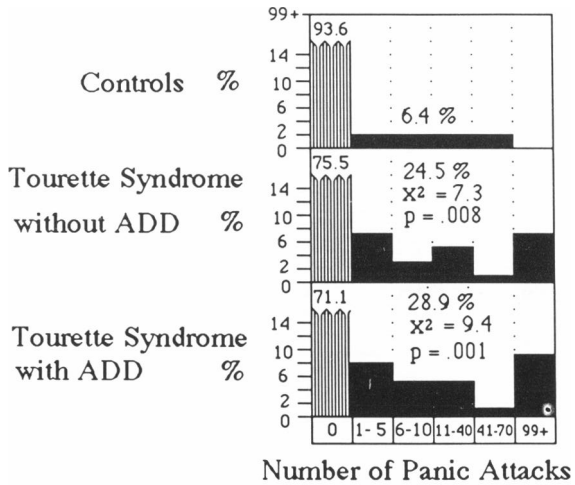


FIG. 2.—Number of panic attacks. *A*, Controls vs. all TS patients, ADD patients, and patients with ADD 2^0 TS; *B*, controls vs. grade 1, grade 2, and grade 3 TS patients; *C*, controls vs. TS patients without ADD and TS patients with ADD. Percentages of patients with one or more panic attacks are given. The χ^2 values are with 1 df.

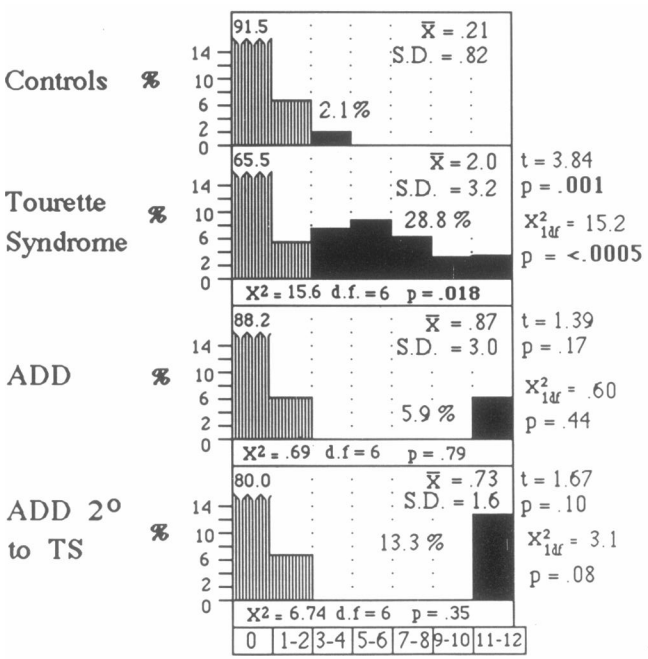
TABLE 3

PANIC-ATTACK SYMPTOMS

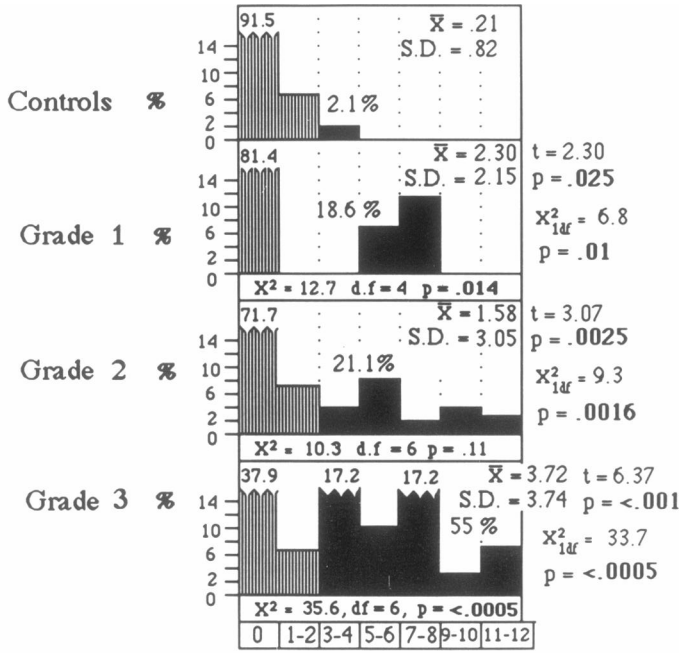
	Diagnostic Category (*N*)								
		TS							
	Controls (47)	All (246)	Grade 1 (43)	Grade 2 (145)	Grade 3 (58)	+ADD (152)	−ADD (94)	ADD (17)	ADD 2⁰ TS (15)
	A. Data for Individual Panic Attacks								
Symptom									
Shortness of Breath:									
%	4.2	17.5	11.6	13.8	31.0	17.7	17.0	6.3	6.7
χ^2	...	5.36	1.72	3.22	12.1	5.27	4.62	0.12	0.16
P	...	.02	.19	.07	<.0005	**.02**	**.03**	.73	.70
Rapid heart beat:									
%	6.3	25.2	16.3	21.4	41.4	25.7	24.5	6.3	6.7
χ^2	...	8.17	2.27	5.55	16.8	8.11	6.90	0.00	0.003
P	...	**.002**	.13	**.02**	**.0005**	**.002**	**.008**	...	.96
Light headedness:									
%	0.0	16.7	4.7	13.8	32.8	15.1	19.2	6.3	6.7
χ^2	...	9.13	2.25	7.24	18.8	8.02	10.3	3.01	3.20
P	...	**.002**	.19	**.007**	**.0005**	**.002**	**.001**	.08	.075
Tingling of extremities:									
%	0.0	13.0	2.3	11.7	24.1	20.0	19.1	6.3	6.7
χ^2	...	6.86	1.09	6.03	13.0	11.1	10.3	3.01	3.20
P	...	**.008**	.29	**.015**	<.0005	**.0008**	**.001**	.08	.075
Tightness in the chest:									
%	0.0	14.2	4.7	11.0	29.3	14.5	13.8	6.3	6.7
χ^2	...	7.58	2.26	5.64	16.4	7.66	7.14	3.01	3.20
P	...	**.006**	.14	**.02**	<.0005	**.005**	**.007**	.08	.075
Choking sensation:									
%	0.0	9.3	4.7	7.6	17.2	9.2	9.6	6.3	0.0
χ^2	...	4.74	2.26	3.79	8.93	4.65	4.82	3.01	3.20
P	...	**.03**	.14	**.05**	**.002**	**.03**	**.03**	.08	...

Faintness:									
%	0.0	10.2	4.7	6.9	22.4	10.5	9.6	6.3	0.0
χ^2	...	5.24	2.25	3.42	12.0	5.36	4.82	3.01	...
P	...	**.02**	.14	.07	**<.0005**	**.02**	**.03**	.08	...
Excessive sweating:									
%	2.1	14.6	9.3	13.1	22.4	13.8	16.0	12.5	6.7
χ^2	...	5.60	2.22	4.61	9.27	5.00	6.00	2.91	0.77
P	...	**.02**	.14	**.03**	**.001**	**.02**	**.015**	.09	.38
Feeling shaky:									
%	4.2	22.7	7.0	17.9	46.5	24.3	20.2	12.5	6.7
χ^2	...	8.52	.33	5.36	23.3	9.22	6.33	1.43	.16
P	...	**.002**	.56	**.02**	**<.0005**	**.0015**	**.01**	.24	.69
Hot flashes:									
%	4.2	16.3	9.3	11.7	32.8	15.8	17.0	6.3	6.7
χ^2	...	4.70	.94	2.25	13.2	4.22	4.62	.12	.16
P	...	**.03**	.33	.14	**<.0005**	**.04**	**.03**	.74	.70
Feeling unreal:									
%	0.0	19.5	9.3	16.5	34.5	15.8	18.1	6.2	6.7
χ^2	...	11.0	4.57	8.86	20.0	8.44	9.67	2.96	3.20
P	...	**.001**	**.03**	**.002**	**<.0005**	**.002**	**.001**	.09	.08
Thinking that one might die:									
%	0.0	18.7	11.6	13.1	37.9	21.7	13.8	6.2	6.7
χ^2	...	10.4	5.77	6.83	22.5	12.2	7.14	2.96	3.20
P	...	**.001**	**.02**	**.008**	**<.0005**	**<.0005**	**.007**	.09	.08
B. Data for Symptoms in Combination									
Average for Symptoms Overall									
%	1.7	16.5	8.0	13.2	31.0	17.0	17.0	7.9	5.6
χ^2	...	7.13	1.98	5.04	15.2	7.25	7.00	1.48	.67
P	...	**.007**	.17	**.02**	**<.0005**	**.007**	**.008**	.23	.41

NOTE.—Significant *P* values are boldface.


Controls %
91.5
2.1%
X̄ = .21
S.D. = .82
Tourette Syndrome %
65.5
28.8 %
X̄ = 2.0
S.D. = 3.2
t = 3.84
p = .001
X²1df = 15.2
p = <.0005
X² = 15.6 d.f. = 6 p = .018
ADD %
88.2
5.9 %
X̄ = .87
S.D. = 3.0
t = 1.39
p = .17
X²1df = .60
p = .44
X² = .69 d.f = 6 p = .79
ADD 2° to TS %
80.0
13.3 %
X̄ = .73
S.D. = 1.6
t = 1.67
p = .10
X²1df = 3.1
p = .08
X² = 6.74 d.f = 6 p = .35
14
10
6
2
0
0 1-2 3-4 5-6 7-8 9-10 11-12
Panic Score

A


Controls %
91.5
2.1%
X̄ = .21
S.D. = .82
Grade 1 %
81.4
18.6 %
X̄ = 2.30
S.D. = 2.15
t = 2.30
p = .025
X²1df = 6.8
p = .01
X² = 12.7 d.f = 4 p = .014
Grade 2 %
71.7
21.1%
X̄ = 1.58
S.D. = 3.05
t = 3.07
p = .0025
X²1df = 9.3
p = .0016
X² = 10.3 d.f = 6 p = .11
Grade 3 %
37.9
17.2
17.2
55 %
X̄ = 3.72
S.D. = 3.74
t = 6.37
p = <.001
X²1df = 33.7
p = <.0005
X² = 35.6, df = 6, p = <.0005
14
10
6
2
0
0 1-2 3-4 5-6 7-8 9-10 11-12
Panic Score

B

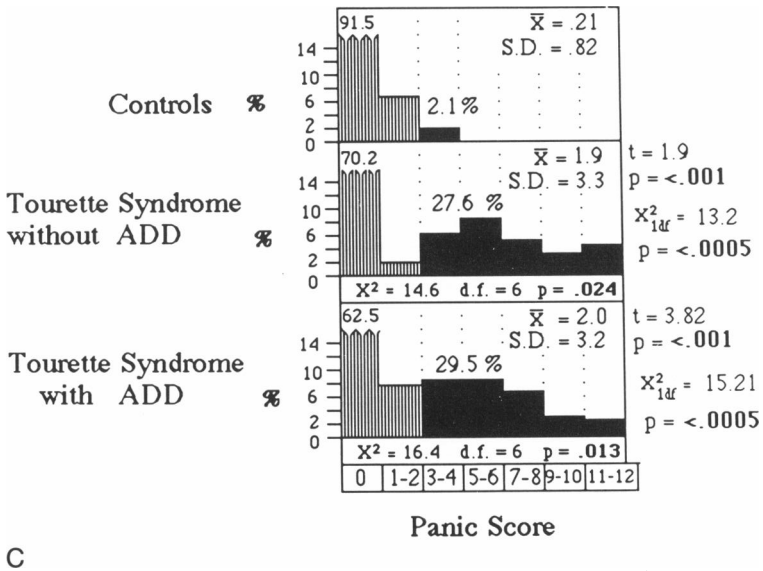


FIG. 3.—Panic-attack scores. *A*, Controls vs. all TS patients, ADD patients, and patients with ADD 2^0 TS. *B*, controls vs. grade 1, grade 2, and grade 3 TS patients; *C*, controls vs. TS patients without ADD and TS patients with ADD. Percentages of patients with a panic score ≥3 are given. Two χ^2 values are given: one with 4 or 6 df, which compares the distribution of the panic scores, and one, $\chi^2_{1\,df}$ (in the right margin), that, using 1 df, compares the percentage of patients with panic scores ≥3. The comparison of the mean panic score by means of the *t*-test is also shown.

TABLE 4

AGE AT ONSET OF PANIC ATTACKS

PARAMETER	DIAGNOSTIC CATEGORY (*N*)						
		TS					
	Controls (3)	All (57)	Grade 1 (4)	Grade 2 (28)	Grade 3 (25)	+ADD (38)	−ADD (19)
Average ± SD years	22.7 ± 10.0	11.0 ± 10.3	14.7 ± 10.7	10.0 ± 11.1	11.4 ± 9.77	8.8 ± 5.76	15.4 ± 15.3
TS vs. controls:							
t	...	1.91	1.00	1.88	1.63	3.83	0.79
P	...	.06	.35	.07	.12	**<.001**	.44
TS with ADD vs. TS without ADD:							
t							2.36
P							**.03**

NOTE.—Significant *P* values are boldface.

controlled with medication. Many of the other phobias, such as fear of being alone, of being in water, of animals, etc., cannot be related to tic-related concerns about public exposure. In addition, there was little correlation between the number of tics and phobias ($r = .14$). When all phobias were considered in combination, there was a significant increase in the number of simple phobias in both the total group of TS patients ($P = .009$) and all grades of TS.

There is very little information on the genetics of simple phobias. They may respond to behavioral therapy and, in contrast to panic attacks, respond poorly to antidepressants. The significantly increased frequency of simple phobias in association with a single-major-gene disorder, TS, indicates that some of them can have a single-gene basis.

Prior to the time that panic attacks were distinguished from generalized anxiety disorder, studies on the genetics of anxiety neuroses included both disorders. Four different reports, dating from 1937 to 1978 (McInnes 1937; Brown 1942; Cohen et al. 1951; Noyes et al. 1978), all agreed that ~15% of first-degree relatives of patients with anxiety neuroses had a similar diagnosis, compared with 1%–3% of the general population. In a study of 142 twins, Slater and Shields (1969) found a concordance rate for marked anxiety of 65% for monozygotic twins, compared with 13% for dizygotic twins.

In more recent studies, the familial occurrence of panic attacks has been specifically examined. Among 12 probands with panic attacks (and mitral valve prolapse), 15.7% of first-degree relatives had panic attacks, compared with only 1.2% of relatives of probands without panic attacks (Crowe et al. 1982). In families that were not selected because of mitral valve prolapse, the gene frequency was estimated at .005. In a study of 19 pedigrees, Pauls et al. (1979*a*, 1979*b*, 1980) concluded that panic attacks were inherited as a dominant trait with incomplete penetrance. However, in a later study of 41 families (Crowe et al. 1983), these investigators were unable to distinguish between single-gene and polygenic inheritance. Among first-degree relatives of patients with panic disorder, 24.7% had panic attacks, compared with 2.2% of controls. Among agoraphobic probands, 31.1% had first-degree relatives who had panic attacks. Of the 41 families, 61% had first-degree relatives who had panic attacks. There was no increase in other psychiatric disorders. In a study of twins, Torgerson (1983) found a concordance rate of 45% in monozygotic twins for all anxiety disorders exclusive of generalized anxiety disorder, compared with 0% for dizygotic twins.

These observations clearly indicate that there is a strong genetic component in the etiology of panic attacks, but they do not distinguish between a major-gene and a polygenic type of inheritance. Since a major-gene mode of inheritance is now well documented for TS (Comings et al. 1984; Devor 1984; Pauls and Leckman 1986), the highly significant association between the presence of a *TS* gene and panic attacks identifies at least one type of major gene in the etiology of panic attacks. As emphasized elsewhere (Comings and Comings 1987*c*), individuals with panic attacks should be questioned about the presence of motor or vocal tics at some time in their life in themselves or family members.

McGrath et al. (1985) have recently described atypical panic attacks that take the form of episodes of rage and respond to treatment with monoamine oxidase inhibitors. Since, as noted in Part II (Comings and Comings 1987*b*), episodic rage attacks are not uncommon in TS, this raises the question of whether these might represent atypical panic attacks. Since panic attacks may be precipitated by lactate infusions (Liebowitz et al. 1984), this question might be answered by determining whether lactate infusions precipitate rage attacks in TS patients.

The highly significant association of panic attacks with the *TS* gene provides the first clear evidence that panic attacks can be due to a major-gene effect.

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